DETAILED ACTION

This action is in response to the amendment, filed 8/30/2010, in which claims 64 and 106 were canceled, and claims 49 and 98 were amended. Claims 49-55, 57, 61-63, 96 and 98-105 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group III with traverse in the reply filed 6/21/2006. Applicant further elected the combination of biomarkers comprising SEQ ID NOs: 1, 2, 5, 15 and 16 (IL-8, COX-2, SAA1, PPAR-alpha and PPAR-gamma, respectively), and the oligonucleotide primers comprising SEQ ID NOs: 45 and 46, which amplify SEQ ID NO: 1; SEQ ID NOs: 47 and 48, which amplify SEQ ID NO: 2; SEQ ID NOs: 53 and 54, which amplify SEQ ID NO: 5; SEQ ID NOs: 73 and 74, which amplify SEQ ID NO: 15; and SEQ ID NOs: 75 and 76, which amplify SEQ ID NO: 16.

In the Office action mailed 9/11/2006, the Examiner withdrew the restriction requirement between Groups III and V. Although the restriction requirement mailed 5/5/2006 required an election of a single invention, which is one combination of sequences, the record indicates that claims reading on less then the full combination of sequences have been examined. Thus, the claims will be considered as they read at least two sequences selected from the group consisting

of SEQ ID NOs: 1, 2 and 5, as well as sequences selected from SEQ ID NOs: 15 and 16. The other combinations of sequences remain withdrawn.

Claims 49-55, 57, 61-63, 96 and 98-105 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 8/24/2010, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Objections

Claim 96 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 96 requires the biomarker to comprise (i) SEQ ID NO: 1, (ii) SEQ ID NO: 2 or (iii) SEQ ID NOs: 1 and 2. However, the independent claim from which claim 96 ultimately depends requires the biomarkers to comprise SEQ ID NOs: 1 and 2. SEQ ID NO: 1 or 2 is not required by some embodiments of claim 96, and those embodiments are broader in scope than the independent claim such that claim 96 does not necessarily include every limitation of the independent claim.

Claims 50 and 99 are objected to because of the following informalities: the claim reads on non-elected invention. Appropriate correction is not required at this time.

Response to Arguments - Claim Objections

The previous objection of claim 49 and dependent claims 50-55, 57, 61-64 and 96 has been withdrawn in view of Applicant's amendment to claim 49 in the reply filed 8/30/2010.

The previous objection of claim 98 and dependent claims 99-106 has been withdrawn in view of Applicant's amendment to claim 98 in the reply filed 8/30/2010.

With respect to the objection of claim 96, Applicant's arguments filed 8/30/2010 have been fully considered but they are not persuasive. The response does not provide specific arguments directed to the objection of claim 96. Therefore, the objection is maintained for the reasons of record.

With respect to the objection of claims 50 and 99, Applicant's arguments filed 8/30/2010 have been fully considered but they are not persuasive. The independent claims are not allowable. Thus, all sequences are not eligible for rejoinder at this time.

Response to Arguments - 35 USC § 112

The rejection of claim 105 under 35 U.S.C. 112, second paragraph, is moot in view of Applicant's cancellation of the claim in the reply filed 8/30/2010.

The rejection of claims 98-105 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to claim 98 in the reply filed 8/30/2010.

The rejection of claim 105 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claim in the reply filed 8/30/2010.

The rejection of claims 98-105 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of Applicant's amendment to claim 98 in the reply filed 8/30/2010.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 49, 54, 55, 57, 61, 96, 98 and 100-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al (Journal of Pathology, Vol. 187, pages 295-301, 1999, cited in a prior action; see the entire reference) in view of Hendel et al (American Journal of Gastroenterology, Vol. 92, No. 7, pages 1170-1173, July 1997; see the entire reference), GenBank Accession No. XM_051900 (GI: 14730543, publicly available July 2001, cited in a prior action; see the entire reference), Brew et al (European Journal of Cancer, Vol. 32A, No. 12, pages 2142-2147, 1996, cited in a prior action; see the entire reference), di Celle et al (Blood, Vol. 84, No. 1, pages 220-228, July 1994, cited in a prior action; see the entire reference), and

GenBank Accession No. XM_031289 (GI: 14731054, publicly available July 2001, cited in a prior action; see the entire reference). This is a new rejection necessitated by the amendment filed 8/30/2010.

Hao et al teach that accumulating evidence suggests that both human and rodent colorectal tumor tissues contain elevated mRNA or protein levels of Cox-2 (e.g., page 295, paragraph bridging columns). Hao et al teach the collection of 85 sporadic colorectal adenomas, 53 colorectal carcinomas, and 19 samples of paired tumor and adjacent grossly normal mucosa (e.g., page 296, left column, 1st and 2nd full paragraph). Hao et al teach selecting Cox-2 as a biomarker; isolating RNA from the samples; and amplifying and quantifying Cox-2 RNA expression by RT-PCR (e.g., page 296, left column, 2nd full paragraph; page 297, left column, 2nd and 3rd full paragraphs; page 297, paragraph bridging columns). Hao et al teach that the step of amplifying further comprises using enzymes and reagents for the preparation of cDNA (e.g., page 297, left column, 3rd full paragraph). Hao et al teach that the step of quantifying the levels of RNA further comprises labeling the amplified polynucleotide with ethidium bromide, which is a chromophore, in an agarose gel, and visualizing the amount of product using ultraviolet fluorescence (e.g., page 297, paragraph bridging columns). Hao et al teach that mRNA for Cox-2 was detected in 3/19 (15.8%) samples of grossly normal mucosa, 5/6 (83.3%) adenomas, and 12/14 (85.7%) carcinomas (e.g., page 298, RT-PCR; Figure 6; Table IV). Hao et al teach that Cox-2 overexpression occurs at an early stage in tumorgenesis, thus indicating an increased risk of transformation (e.g., page 295, paragraph bridging columns; page 299, paragraph bridging columns; page 300, left column, 2nd full paragraph).

Hao et al do not teach the comparison of Cox-2 mRNA expression levels in the

macroscopically normal mucosa to a normal control colorectal sample from a subject without colorectal carcinoma. Hao et al do not teach that Cox-2 has the sequence of SEQ ID NO: 2. Hao et al do not teach amplifying, quantifying and comparing the expression of SEQ ID NO: 1 (IL-8) in the colorectal samples. Hao et al do not teach obtaining a sample of colorectal cells by a minimally invasive technique.

Hendel et al teach the collection of a mucosal biopsy during endoscopy of 11 patients with a normal proctoscopy to provide control samples (e.g., paragraph bridging pages 1170-1171). Hendel et al teach extracting RNA from the biopsy tissue, reverse transcribing the RNA to provide cDNA, and amplifying the cDNA by PCR (e.g., page 1171, left column). Hendel et al teach quantifying the levels of RNA by labeling the amplified polynucleotide with ethidium bromide in an agarose gel and visualizing the amount of product using ultraviolet fluorescence (e.g., page 1171, right column, *Gel analysis*). Hendel et al teach that Cox-2 mRNA is not expressed in healthy controls without endoscopic inflammatory activity (e.g., Table 1; Figure 1).

GenBank Accession No. XM_051900 teaches the sequence of human Cox-2 (a.k.a. prostaglandin-endoperoxide synthase 2). This sequence is identical to instant SEQ ID NO: 2 (see the alignment in Appendix I, mailed 3/5/2010).

Brew et al teach that IL-8 production was known to be a feature of certain human tumor cell lines derived from colon carcinoma (e.g., page 2143, left column, 1st paragraph). Brew et al teach the collection of tissue samples of normal colon, neoplastic colorectal and adjoining non-involved tissue, and lymph node metastasis (e.g., page 2143, left column, 2nd paragraph). Brew et al teach the construction of sense and antisense riboprobes to the IL-8 cDNA for use in *in situ* hybridization to quantify the level of IL-8 RNA expression in the collected tissue samples (e.g.

page 2143, left column, 4th paragraph and right column, 1st paragraph). Brew et al teach that all 10 adenocarcinoma samples, including a lymph node metastasis, showed cytoplasmic hybridization with the IL-8 probe, and the intensity of staining ranged from weak to strong (e.g., paragraph bridging pages 2143-2144; Table 1). Further, Brew et al compared the level of IL-8 RNA expression in the adenocarcinomas to the expression in normal colonic mucosa, and determined that expression was increased in the adenocarcinoma relative to the normal colonic mucosa, which showed much weaker staining or was completely negative (e.g., paragraph bridging pages 2143-2144).

Di Celle et al teach a sensitive reverse-transcriptase polymerase chain (RT-PCR) analysis performed to evaluate the expression of a panel of cytokine mRNAs in unstimulated B-LL cells, where the panel includes IL-8 (e.g., page 220, paragraph bridging columns). Di Celle et al teach RT-PCR of IL-8 from total cellular RNA followed by analysis in gels stained with ethidium bromide (e.g., page 221, right column, full paragraph). Di Celle et al teach that the IL-8 mRNA can be quantified relative to a co-amplified gene (e.g., paragraph bridging pages 222-224). Di Celle et al teach that IL-8 mRNA expression is increased in a variety of cancer types (e.g., page 226, left column), and that evaluation of cytokine production can help to better understand processes that govern proliferation and growth (e.g., page 227, left column, 1st full paragraph).

GenBank Accession No. XM_031289 teaches the sequence of human IL-8 transcript. This sequence is identical to instant SEQ ID NO: 1 (see the alignment in Appendix II, mailed 3/5/2010).

Hao et al teach that Cox-2 RNA expression is an early event in colorectal cancer. Because Hao et al teach expression of Cox-2 RNA in normal appearing mucosa from subjects

with colorectal cancer, and Hendel et al teach that Cox-2 RNA is not expressed in healthy subjects without colorectal cancer or inflammation, one of skill in the art would have recognized that subject with detectable Cox-2 RNA expression in a sample of normal appearing colon would be at increased risk of colorectal cancer. The association between Cox-2 expression and colorectal cancer was known in the art (e.g., Hao et al.), and the absence of expression in healthy, normal subjects was also known in the art (Hendel et al.). One would have been motivated to make such a comparison to identify subjects at risk of developing colorectal cancer at a later point since Cox-2 expression is an early event in the development of colorectal cancer. Furthermore, it would have been obvious to collect the samples with minimally invasive technique, such as the biopsy during endoscopy taught by Hendel et al, because one would want to use a known technique for the collection of samples. One would have been motivated to use the biopsy taken during endoscopy, because it is a less invasive technique than collecting a biopsy during surgery, for example.

Because Hao et al teach amplifying and quantifying Cox-2 RNA expression in human cells, and GenBank Accession No. XM_051900 teaches the Cox-2 sequence transcribed in humans, it would have been within the skill of the art to substitute the specific sequence of XM_051900 for the sequence used by Hao et al in order to achieve the predictable result of amplifying and quantifying Cox-2 RNA expression in human cells.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the assay of Hao et al and Hendel et al to include the measurement of IL-8 RNA expression in the colorectal samples, as taught by Brew et al, using the method of di Celle et al. Hao et al and Hendel et al teach it is within the ordinary skill in the

art to use RT-PCR to detect RNA expression of a gene increased in expression in normal appearing mucosa, and Brew et al teach the quantification of IL-8 RNA expression in colorectal cancer and normal mucosa. Furthermore, di Celle et al teach the quantification of IL-8 mRNA expression by RT-PCR. Thus, it would have been obvious to combine the quantification of Cox-2 RNA expression and IL-8 RNA expression in the same samples using the same type of RT-PCR assay. Moreover, it would have been obvious to one of ordinary skill in the art to substitute the specific sequence of XM_031289 for the sequence of IL-8, because both Brew et al and di Celle et al teach the measurement of IL-8 expression in human cells, and XM_032189 provides the sequence of the human IL-8 transcript.

One would have been motivated to make such a modification in order to receive the expected benefit of furthering the understanding of IL-8 expression in colorectal carcinoma, colorectal adenoma, and normal mucosa as taught by Brew et al, and suggested by di Celle et al with regard to proliferative disease and cancer. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 50, 51 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al (Journal of Pathology, Vol. 187, pages 295-301, 1999, cited in a prior action; see the entire reference) in view of Hendel et al (American Journal of Gastroenterology, Vol. 92, No. 7, pages 1170-1173, July 1997; see the entire reference), GenBank Accession No. XM_051900 (GI: 14730543, publicly available July 2001, cited in a prior action; see the entire reference), Brew et al (European Journal of Cancer, Vol. 32A, No. 12, pages 2142-2147, 1996, cited in a prior

action; see the entire reference), di Celle et al (Blood, Vol. 84, No. 1, pages 220-228, July 1994, cited in a prior action; see the entire reference), and GenBank Accession No. XM_031289 (GI: 14731054, publicly available July 2001, cited in a prior action; see the entire reference) as applied to claims 49, 54, 55, 57, 61, 96, 98 and 100-103 above, and further in view of DuBois et al (Carcinogenesis, Vol. 19, No. 1, pages 49-53, 1998, cited in a prior action; see the entire reference), Park et al (Diabetes, Vol. 46, No. 7, pages 1230-1234, July 1997, cited in a prior action; see the entire reference) and GenBank Accession No. XM_003059 (GI: 13646004, publicly available April 2001, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment filed 8/30/2010.

The combined teachings of Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 are described above and applied as before.

Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 do not teach the method further comprising amplifying and quantifying RNA expression, and comparing the quantified expression levels in a colorectal sample from a normal appearing mucosa from a subject and a control for SEQ ID NO: 16 (PPARG).

DuBois et al teach that they previously demonstrated increased COX-2 expression in human colorectal adenocarcinomas when compared to normal adjacent colonic mucosa, and these findings have been confirmed by other investigators who have shown elevated levels of COX-2 protein in colorectal tumors by immunoblotting, and immunohistochemical staining (e.g., page 49, right column, full paragraph). DuBois et al teach that COX-2 mRNA and protein

expression has also been found to be increased in intestinal tumors that develop in rodents following carcinogen treatment and in adenomas taken from *Min* mice (e.g., page 49, right column, full paragraph). DuBois et al teach that COX-2 overexpression in rat intestinal epithelial cells leads to phenotypic alterations, such increase tumorigenic potential, and the phenotypic alterations can be reversed by treatment with highly selective COX-2 inhibitors (e.g., paragraph bridging page 49-50). DuBois et al teach that the eicosanoid products formed by the COX-2 enzyme are likely affecting downstream signaling pathways, ultimately regulating gene transcription, and one candidate for eicosanoid mediated transcriptional regulation is the PPARγ nuclear receptor (e.g., paragraph bridging pages 49-50). Based upon this rationale, DuBois et al undertook studies to determine if PPARγ is aberrantly expressed in colon tumor cells and found that PPARγ mRNA and protein was expressed in intestinal tumor, and a subset of polyps and human colon cancer cell lines (e.g., paragraph bridging pages 49-50; page 50, paragraph bridging columns; page 51, right column, 1st full paragraph). Figure 1 shows the expression of PPARγ and COX-2 in normal control colorectal tissue and colorectal tumor tissue from rats. Based upon the data from rats, DuBois et al hypothesized that PPARγ would be expressed in human colon cancer cells as well (e.g., page 51, right column, 1st full paragraph). DuBois et al measured the expression of PPARγ in the human colon cancer cell lines and determined that some of the cells lines express PPARγ (e.g., page 51, right column, 1st full paragraph; Figure 4). DuBois et al teach that work was underway to determine the biological relevance of aberrant co-expression of PPARγ and COX-2 (e.g., page 52, paragraph bridging columns).

Park et al teach it is within the skill of the art to measure increased PPARγ mRNA expression in human cells by RT-PCR (e.g., pages 1231-1232, Reverse transcription-polymerase

chain reaction (RT-PCR) of PPAR-γ). Further, Park et al teach that the tissue specificity, relative abundance, and regulation of expression of PPARγ in human tissues need to be defined to address the physiological function of PPARγ (e.g., page 1230, right column).

GenBank Accession No. XM_003059 teaches the sequence of human PPARγ transcript. This sequence is identical to instant SEQ ID NO: 16 (see the alignment in Appendix III, mailed 3/5/2010).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combined teachings of Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 to include the quantitative RT-PCR assay for PPARγ taught by Park et al in the normal appearing colorectal samples from the subject and control. DuBois et al teach a potential relationship between COX-2 RNA expression and PPARγ RNA expression in colorectal cancer, and Park et al teach it is desirable to quantitate PPARγ RNA expression to address the physiological function of PPARγ. Furthermore, it would have been obvious to one of ordinary skill in the art to substitute the specific sequence of XM_003059 for the sequence of PPARγ, because both DuBois et al and Park et al teach the measurement of PPARγ expression in human cells, and XM_003059 provides the sequence of the human PPARγ transcript.

One would have been motivated to make such a modification in order to receive the expected benefit of better understanding the expression of PPARγ RNA in normal human colorectal tissue, human colorectal adenomas and human colorectal carcinoma, as it relates to Cox-2 RNA expression in the same cells. Based upon the teachings of the cited references, the

high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al (Journal of Pathology, Vol. 187, pages 295-301, 1999, cited in a prior action; see the entire reference) in view of Hendel et al (American Journal of Gastroenterology, Vol. 92, No. 7, pages 1170-1173, July 1997; see the entire reference), GenBank Accession No. XM_051900 (GI: 14730543, publicly available July 2001, cited in a prior action; see the entire reference), Brew et al (European Journal of Cancer, Vol. 32A, No. 12, pages 2142-2147, 1996, cited in a prior action; see the entire reference), di Celle et al (Blood, Vol. 84, No. 1, pages 220-228, July 1994, cited in a prior action; see the entire reference), and GenBank Accession No. XM_031289 (GI: 14731054, publicly available July 2001, cited in a prior action; see the entire reference) as applied to claims 49, 54, 55, 57, 61, 96, 98 and 100-103 above, and further in view of DuBois et al (Carcinogenesis, Vol. 19, No. 1, pages 49-53, 1998, cited in a prior action; see the entire reference), Park et al (Diabetes, Vol. 46, No. 7, pages 1230-1234, July 1997, cited in a prior action; see the entire reference) and GenBank Accession No. XM_003059 (GI: 13646004, publicly available April 2001, cited in a prior action; see the entire reference) as applied to claims 49-51, 53-55, 57, 61, 96, 98, 99 and 100-103 above, and further in view of Baker et al (WO 2003/078662 A1, cited in a prior action; see the entire reference) and Gould et al (Kidney International, Vol. 61, pages 51-60, January 2002, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the amendment filed 8/30/2010.

The teachings of Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, GenBank Accession No. XM_031289, DuBois et al, Park et al, and GenBank Accession No. XM_003059 are described above and applied as before.

Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, GenBank Accession No. XM_031289, DuBois et al, Park et al, and GenBank Accession No. XM_003059 do not teach the method where the step of amplifying further comprises using primers of SEQ ID NO: 47 and 48 for Cox-2, and primers of SEQ ID NO: 45 and 46 for IL-8.

Baker et al teach a panel of two or more gene specific primers selected from the group consisting of the forward and reverse primers listed in Table 2 (e.g., page 18, lines 3-4). Table 2 contains forward and reverse primers for COX2 (PTGS2), which consist of SEQ ID NOs: 229 and 230 (e.g., Table 2 at page 72). The sequences of Baker et al, SEQ ID NOs: 229 (5'-TCTGCAGAGTTGGAAGCACTCTA-3') and 230 (5'-GCCGAGGCTTTTCTACCAGAA-3') consist of sequences 100% identical to the claimed sequences of SEQ ID NOs: 47 and 48 (e.g., page 29 of the sequence listing of Baker et al). Baker et al teach that the primers may be used for gene expression profiling using RT-PCR preceded by an amplification step (e.g., page 5, lines 22-27; page 7, lines 7-9 and 25). Further, Baker et al teach RT-PCR of IL8 (e.g., page 8, lines 31-33). Baker et al teach further reagents for RT-PCR, including reagents for the preparation of cDNA, such as the GeneAmp RNA PCR kit; and reagents for the detection and quantitation of polynucleotides that contain at least one chromophore, such as components for TaqMan PCR® where the probe is designed to detect a nucleotide sequence between the two primers and is labeled with a reporter fluorescent dye (e.g., pages 31-32). Baker et al teach that RT-PCR is a flexible and quantitative method that can be used to compare mRNA levels in different sample

populations, tumor tissues, including colon cancer, and corresponding normal tissues to characterize patters of gene expression (e.g., page 4, lines 14-18; page 5, lines 18-21; page 7, lines 12-16; page 31, lines 12-18; page 31, lines 8-11).

Gould et al teach oligonucleotides to be used as primers for RT-PCR of IL8 (e.g., Table 1). The forward primer for IL8 is 5'-AGATATTGCACGGGAGAATATACAAA-3', and the reverse primer for IL8 is 5'-TCAATTCCTGAAATTAAAGTTCGGATA-3' (Table 1). The primer sequences taught by Gould et al consist of a nucleic acid sequence 100% to SEQ ID NOs: 45 and 46.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combined teaches teachings to include the specific primer sequences taught by Baker et al and Gould et al because Hao et al, di Celle et al and Baker et al teach it is within the ordinary skill in the art to use primers for RT-PCR to quantify the RNA expression levels of Cox-2 and IL-8.

One would have been motivated to make such a modification in order to receive the expected benefit of using primers known in the art to successfully amplify Cox-2 and IL-8 as taught by Baker et al and Gould et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 62 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al (Journal of Pathology, Vol. 187, pages 295-301, 1999; see the entire reference) in view of Hendel et al (American Journal of Gastroenterology, Vol. 92, No. 7, pages 1170-1173, July

1997; see the entire reference), GenBank Accession No. XM_051900 (GI: 14730543, publicly available July 2001; see the entire reference), Brew et al (European Journal of Cancer, Vol. 32A, No. 12, pages 2142-2147, 1996; see the entire reference), di Celle et al (Blood, Vol. 84, No. 1, pages 220-228, July 1994; see the entire reference), and GenBank Accession No. XM_031289 (GI: 14731054, publicly available July 2001; see the entire reference) as applied to claims 49, 54, 55, 57, 61, 96, 98 and 100-103 above, and further in view of Melville et al (Journal of Clinical Pathology, Vol. 41, pages 1180-1186, 1988; see the entire reference), and Ristimäki et al (US Patent No. 6,416,961 B1; see the entire reference). This is a new rejection, necessitated by the amendment filed 8/30/2010.

The combined teachings of Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 are described above and applied as before.

Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 do not teach the method where the colorectal cells are obtained by the use of a swab.

Melville et al teach that brush cytology (i.e., swabbing) through a colonoscope has been shown to have a high accuracy in the diagnosis of colorectal cancer and has been recommended in the diagnosis of colonic strictures (e.g., page 1180, paragraph bridging columns). Melville et al teach the collection of cytology brushings during colonoscopy either with a standard sheathed 10 mm x 3 mm reusable colonoscopy brush, or in some cases a disposable brush (e.g., page 1181, left column, 2nd full paragraph). For brushings taken through a rigid sigmoidoscope, a brush with a rounded end was designed which could easily be rotated on the mucosa and which

brushed an area of about 3 cm^2 (e.g., page 1181, paragraph bridging columns). Melville et al teach that neoplastic changes can be observed in cells collected by cytology brushing (e.g., page 1185, right column, 4th paragraph).

Ristimäki et al acknowledge that recent studies show that Cox-2 is connected to colon carcinogenesis (e.g., paragraph bridging columns 1-2). Ristimäki et al teach that increased Cox-2 RNA expression can be detected in patient samples obtained as biopsies or brush samples, which are obtained during routine gastroscopy or gastric lavage combined with brush technique (e.g., column 3, lines 21-23). Ristimäki et al teach that the brush technique is well known in the art in routine gastric cytology, and the technique provides cell samples from the gastric mucosa for microscopic examination, and markers, such as Cox-2 RNA, may increase the sensitivity and specificity of the assay (e.g., column 3, lines 24-33). Ristimäki et al teach that Cox-2 mRNA can be conveniently detected from the brush samples using methods known in the art, such as RT-PCR (e.g., column 3, lines 13-38).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combined teaches, such that sample collection of colorectal cells is performed by swabbing with a brush during colonoscopy or sigmoidoscopy as taught by Melville et al, because Melville et al teach it is within the ordinary skill in the art to use a brush to collect colorectal cells and Ristimäki et al teach the use of cells obtained by brushing to detect levels of Cox-2 RNA expression, which is consistent with the combined teachings of the references and goal of providing levels of Cox-2 expression to evaluate risk of colorectal carcinoma.

One would have been motivated to make such a modification in order to receive the expected benefit of using a less invasive method as compared to the biopsy method taught by

Hao et al to achieve the same result of providing cells for the analysis of RNA expression as taught by Ristimäki et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 61, 63, 103 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hao et al (Journal of Pathology, Vol. 187, pages 295-301, 1999; see the entire reference) in view of Hendel et al (American Journal of Gastroenterology, Vol. 92, No. 7, pages 1170-1173, July 1997; see the entire reference), GenBank Accession No. XM_051900 (GI: 14730543, publicly available July 2001; see the entire reference), Brew et al (European Journal of Cancer, Vol. 32A, No. 12, pages 2142-2147, 1996; see the entire reference), di Celle et al (Blood, Vol. 84, No. 1, pages 220-228, July 1994; see the entire reference), and GenBank Accession No. XM_031289 (GI: 14731054, publicly available July 2001; see the entire reference) as applied to claims 49, 54, 55, 57, 61, 96, 98 and 100-103 above, and further in view of Davidson et al (Cancer Epidemiology, Biomarkers & Prevention, Vol. 4, pages 643-647, September 1995; see the entire reference). This is a new rejection, necessitated by the amendment filed 8/30/2010.

The combined teachings of Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 are described above and applied as before.

Hao et al, Hendel et al, GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 do not teach the method where the colorectal cells are obtained by non-invasive collection of a stool sample.

Davidson et al teach that approximately one-sixth to one-third of normal adult colonic epithelial cells are shed every day (e.g., page 643, right column, 1st full paragraph). Davidson et al teach that the number of intact cells isolated from fecal material is lower than the number of total cells shed; thus, an enhanced detection system is required to amplify potential intermediate biomarkers of colon cancer (e.g., page 643, right column, 1st full paragraph). Davidson et al teach such an enhanced detection system, which requires the use of semi-quantitative "mimic" RT-PCR to detect the expression of genes with potential diagnostic value in the colon (e.g., page 643, right column, 1st full paragraph; pages 643-644, Materials and Methods). Davidson et al teach that this approach provides a sensitive method for detection of mRNA isolated from feces containing exfoliated colonocytes and a noninvasive means for monitoring changes in this population of cells (e.g., page 643, right column, 1st full paragraph). Davidson et al teach that their analysis of protein kinase C mRNA expression in shed colonocytes was consistent with previous results obtained from scraped colonic mucosa (e.g., page 646, left column, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combined teaches, such that sample collection of colorectal cells is performed by collecting a fecal sample as taught by Davidson et al, because Davidson et al teach that normal colorectal cells are normally shed into the feces, and it is within the skill of the art to isolate RNA from these cells, and measure gene expression using RT-PCR. Further, Davison et al teach that the procedure may be applied to the quantitation of colon cancer biomarkers, which is consistent with the combined teachings of the references and goal of providing levels of Cox-2 RNA expression to evaluate risk of colorectal carcinoma.

One would have been motivated to make such a modification in order to receive the expected benefit of using a less invasive method as compared to the biopsy method taught by Hao et al to achieve the same result of providing cells for the analysis of RNA expression as taught by Davidson et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 49, 54, 55, 57, 61, 63, 64, 96, 98, 100-103, 105 and 106 under 35 U.S.C. 103(a) as being unpatentable over Kanaoka et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/30/2010.

The rejection of claims 50, 51 and 99 under 35 U.S.C. 103(a) as being unpatentable over Kanaoka et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289, and further in view of DuBois et al, Park et al and GenBank Accession No. XM_003059 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/30/2010.

The rejection of claims 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Kanaoka et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289, and further in view of DuBois et al, Park et al and GenBank Accession No. XM_003059, and further in view of Baker et al and Gould et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/30/2010.

The rejection of claims 49, 54, 55, 57, 96, 98 and 100-102 under 35 U.S.C. 103(a) as being unpatentable over Hao et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/30/2010.

The rejection of claims 50, 51 and 99 under 35 U.S.C. 103(a) as being unpatentable over Hao et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289, and further in view of DuBois et al, Park et al and GenBank Accession No. XM_003059 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 8/30/2010.

The rejection of claims 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Hao et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289, and further in view of DuBois et al, Park et al and GenBank Accession No. XM_003059, and further in view of Baker et al and Gould et al has been withdrawn in view of Applicant's amendment to the claims.

The rejection of claims 61, 62, 103 and 104 under 35 U.S.C. 103(a) as being unpatentable over Hao et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289, and further in view of Melville et al, and Ristimäki et al has been withdrawn in view of Applicant's amendment to the claims.

The rejection of claims 61, 63, 64, 103, 105 and 106 under 35 U.S.C. 103(a) as being unpatentable over Hao et al in view of GenBank Accession No. XM_051900, Brew et al, di Celle et al, and GenBank Accession No. XM_031289, and further in view of Davidson et al has been withdrawn in view of Applicant's amendment to the claims.

Applicant's arguments filed 8/30/2010 have been fully considered but they are not persuasive.

The response points to pages 5-14 of the prior action and notes that it was indicated that there is a difference between diagnosing and determining risk. Based upon this discussion, Applicant asserts that the teachings of the cited references not enabled for determining a risk.

This argument is not found persuasive. The present specification defines the difference between diagnosis and risk assessment at paragraph [0029]:

> The difference between risk assessment and early detection is the degree of certainty regarding acquiring CRC. Biomarkers that are used for risk assessment confer less than 100% certainty of CRC within a time interval, whereas biomarkers used for early detection confer an almost 100% certainty of the onset of the disease within a specified time interval.

Hao et al teach that Cox-2 expression is an early even in the development of colorectal cancer and teach that Cox-2 expression can be detected in normal appearing mucosa in subject with colorectal cancer. Hendel et al teach that Cox-2 expression is not detected in normal appearing mucosa of healthy subjects without colorectal cancer. Thus, one would have recognized that increased expression of Cox-2 would be indicative of increased risk of colorectal cancer. However, Hendel et al teach that Cox-2 expression is present in inflammatory lesions of subjects with inflammatory bowel disease. Thus, the presence of Cox-2 expression might be indicative of inflammation rather than cancer. Using the teachings of the specification directed to diagnosis and risk, one would have recognized that Cox-2 expression could not be used for diagnosis (there would be uncertainty as to whether the subject would develop colorectal cancer or inflammatory bowel disease) but could be used for risk assessment. 100% certainty is not required for risk

assessment (specification, paragraph [0029]). Thus, the references cited in the above rejections are enabled for risk assessment.

The response asserts that the references do not teach or suggest obtaining a biological sample from normal appearing mucosa.

This argument is not found persuasive. Both Hao et al and Hendel et al teach the collection of samples from normal appearing colonic mucosa.

The response comments on the number of references used to reject the claims.

In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636